

Adequacy of a Questionnaire for Evaluation of Radiopharmaceuticals-related Adverse Events: Cross-cultural Adaptation

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Adequação de Questionário para Avaliação de Eventos Adversos Relacionados a Radiofármacos: Adaptação Transcultural
Adecuación del Cuestionario para la Evaluación de Eventos Adversos Relacionados con los Radiofármacos: Adaptación Transcultural

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ABSTRACT

Introduction: Radiopharmaceuticals cause few adverse events that usually are underreported, negatively impacting the guidance provided to users. The lack of a specific tool for assessing radiopharmaceuticals adverse reactions in the patients' perspective is a reality in Brazil. **Objective:** To carry out a cross-cultural adaptation and adapt a questionnaire to assess self-reported adverse events of radiopharmaceuticals by users of nuclear medicine. **Method:** Study of cultural appropriation and adequacy of the questionnaire carried out in a reference cancer hospital. **Results:** Translation, synthesis and backtranslation of the questionnaire titled 'Experiences with Nuclear Medicine Examinations' were performed. After this step, the entire process was analysed by eight expert judges who issued their informed opinions. Subsequently, ten users of the nuclear medicine service analysed the questionnaire and, based on the problems identified, the Delphi technique was implemented with ten experts. After a consensus was reached on the clarity and pertinence of the questions, the final version of the tool was created and applied to 211 participants, 18 of which reported at least one adverse event. Two of these were classified as possible and five as probable, according to the Silberstein causality. **Conclusion:** After the cross-cultural adaptation of the instrument to Portuguese, it was possible to apply it and obtain a satisfactory response about radiopharmaceuticals related adverse events.

Key words: Validation Study; Radiopharmaceuticals; Adverse Event; Nuclear Medicine; Patient Safety.

RESUMO

Introdução: Os radiofármacos geram poucos eventos adversos, havendo subnotificações e consequentemente falha nas orientações fornecidas aos usuários. A falta de ferramenta específica para avaliação de reações adversas a radiofármacos na perspectiva dos pacientes é uma realidade no Brasil. **Objetivo:** Realizar a adaptação transcultural e adequar um questionário para avaliação de eventos adversos relacionados a radiofármacos autorrelatados pelos usuários do serviço de medicina nuclear. **Método:** Estudo de apropriação cultural e adequação de questionário realizado em hospital de referência em câncer. **Resultados:** Foram realizadas a tradução, a síntese e a tradução reversa do questionário 'Experiences with Nuclear Medicine Examinations'. Após essa etapa, todo o processo foi analisado por oito juízes especialistas, os quais emitiram pareceres com as observações pertinentes. Posteriormente, dez usuários do serviço de medicina nuclear analisaram o questionário e, a partir dos problemas identificados, realizou-se a técnica Delphi com dez especialistas. Após o consenso com relação à clareza e à pertinência das perguntas, construiu-se a versão final da ferramenta. Em seguida, esta foi aplicada a 211 participantes. Dezoito relataram pelo menos um evento adverso. Dois destes foram classificados como possíveis e cinco como prováveis de acordo com a causalidade de Silberstein. **Conclusão:** Após a adaptação transcultural do instrumento para o idioma português, foi possível aplicá-lo e ter resposta satisfatória quanto à identificação de eventos adversos a radiofármacos.

Palavras-chave: Estudo de Validação; Compostos Radiofarmacêuticos; Evento Adverso; Medicina Nuclear; Segurança do Paciente.

RESUMEN

Introducción: Los radiofármacos generan pocos efectos adversos, pero se notifican de forma insuficiente y, en consecuencia, las orientaciones proporcionadas a los usuarios son deficientes. La falta de una herramienta específica para evaluar las reacciones adversas a los radiofármacos desde la perspectiva de los pacientes es una realidad en el Brasil. **Objetivo:** Realizar la adaptación transcultural y adaptar un cuestionario para evaluar los eventos adversos relacionados con los radiofármacos autodeclarados por los usuarios del servicio de medicina nuclear. **Método:** Estudio de apropiación cultural y adaptación de un cuestionario realizado en hospital de referencia en cáncer. **Resultados:** Se llevó a cabo la traducción, síntesis y retrotraducción del cuestionario 'Experiences with Nuclear Medicine Examinations'. Todo el proceso fue analizado por ocho jueces expertos, que emitieron dictámenes con las observaciones pertinentes. Posteriormente, diez usuarios del servicio de medicina nuclear analizaron el cuestionario y, a partir de los problemas identificados, se aplicó la técnica Delphi con diez especialistas. Tras alcanzar un consenso sobre la claridad y pertinencia de las preguntas, se elaboró la versión final de la herramienta. A continuación, se aplicó a 211 participantes. Dieciocho informaron de al menos un evento adverso. Dos de ellos se clasificaron como posibles y cinco como probables, de acuerdo con la causalidad de Silberstein. **Conclusión:** Tras la adaptación transcultural del instrumento al idioma portugués, fue posible aplicarlo y obtener una respuesta satisfactoria en cuanto a la identificación de eventos adversos a los radiofármacos.

Palabras clave: Estudio de Validación; Radiofármacos; Evento Adverso; Medicina Nuclear; Seguridad del Paciente.

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INTRODUCTION

Diagnostical or therapeutical radiopharmaceuticals are radioactive compounds that can cause unexpected adverse events difficult to determine the cause¹, partially because most of them are minor (RAM-R)² and notifications are scarce. Although rare compared to other drugs, these reactions should be monitored because they can be severe and compromise the treatment and the patient's life³. Due to the increased use of radiopharmaceuticals in treatment, health professionals should be aware of the incidence of adverse reactions⁴.

It is possible to evaluate the safety of radiopharmaceuticals and circumvent the sub-notification based on patients-reported adverse reactions according to articles that developed self-reported questionnaires to help the detection of RAM-R^{6,7}. Schreuder et al.⁷ developed and validated a useful self-reported identification tool of radiopharmaceuticals-induced adverse events.

Health professionals, patients and the society can see similar diseases differently leading to diverse types of care. Intercountry comparisons should utilize equivalent – and not identical – standard measures of health evaluation due to cultural differences. The cultural scenario translates into different words, idiomatic expressions and colloquialism usually understood in another environment but far from the standard language. Two steps should be clearly distinguished in the cross-cultural development of an instrument of health status: cross-cultural adaptation, comprising the translation in standard language plus the adjustment of cultural words, idioms and context, possibly involving the complete transformation of some items in order to capture the same context and the validation of the transformed instrument^{8,9}. The objective of the present study is the cross-cultural adaptation of an investigational patient-reported radiopharmaceutical-related adverse events questionnaire of nuclear medicine and further application in medication users.

METHOD

Cross-cultural adaptation of a self-reported questionnaire of radiopharmaceuticals adverse events performed at a nuclear medicine service of an oncology reference hospital. The cross-cultural adaptation of the tool 'Experiences with Nuclear Medicine Examinations', developed and validated by Schreuder et al.⁷ was performed after the authors approved its utilization. The issues related to the quality of life were obtained from the questionnaire of the group EuroQol (EQ-5D-3L) translated and validated into Portuguese¹⁰.

The present study was divided in three steps: cross-cultural adaptation, review by experts and users of radiopharmaceuticals and application of the tool (Figure 1).

The text was translated into Portuguese, synthesized and back-translated into English. Two English-fluent translators whose origin language was Portuguese translated the instrument in versions 1 and 2, only one of them was a nuclear medicine expert.

An independent, non-expert individual joined the team as mediator of the translation discrepancies to reach a common translation, and produced a document containing the justification of the synthesis (version 12).

Two different translators fluent in Portuguese whose origin language was English back-translated the instrument to check the validity of version 12, creating versions 21 and 21'. As in the initial translation, one of them was not a nuclear medicine expert.

A panel of ten nuclear medicine expert judges reviewed the translation and cross-cultural adaptation, including the original, translation, synthesis of the translations and back-translation in addition to specific instructions for analysis and evaluation. Reports with recommendations have been prepared to obtain semantic, idiomatic, cultural and conceptual equivalence⁹. The version 3 of the instrument was produced after reviewing and analyzing all the participants inputs of this stage.

Ten users of nuclear medicine other than health professionals were invited to verify the accuracy of version 3 of the questionnaire. The inclusion criteria for this stage were users able to read and speak Portuguese, without cognitive deficit and older than 18 years of age¹¹. A 0-5 Likert-scale was included to check the accuracy of the questions, where 0 indicated "did not understand at all" and 5, "fully understood and have no doubts". Responses lower or equal to three reflected unsatisfactory understanding¹².

After the users evaluated the questionnaire, ten nuclear medicine experts, other than those who participated of the content evaluation phase, were invited to produce the Delphi-based final questionnaire¹³. The experts evaluated the items of the construct and whether the content matched the objectives.

For each item of the questionnaire, the expert responded to the following questions: "In your opinion, is this item/question CLEAR enough to be understood by the target-population?" and "Is this item/question PERTINENT to the study and to the target-population?". The response followed the 5-point Likert-scale, being 1 scarcely clear/pertinent and 5, very clear/pertinent. There was an open field for comments in each question. The questionnaire was deemed satisfactory if consensus was higher or equal to 70%¹⁴.

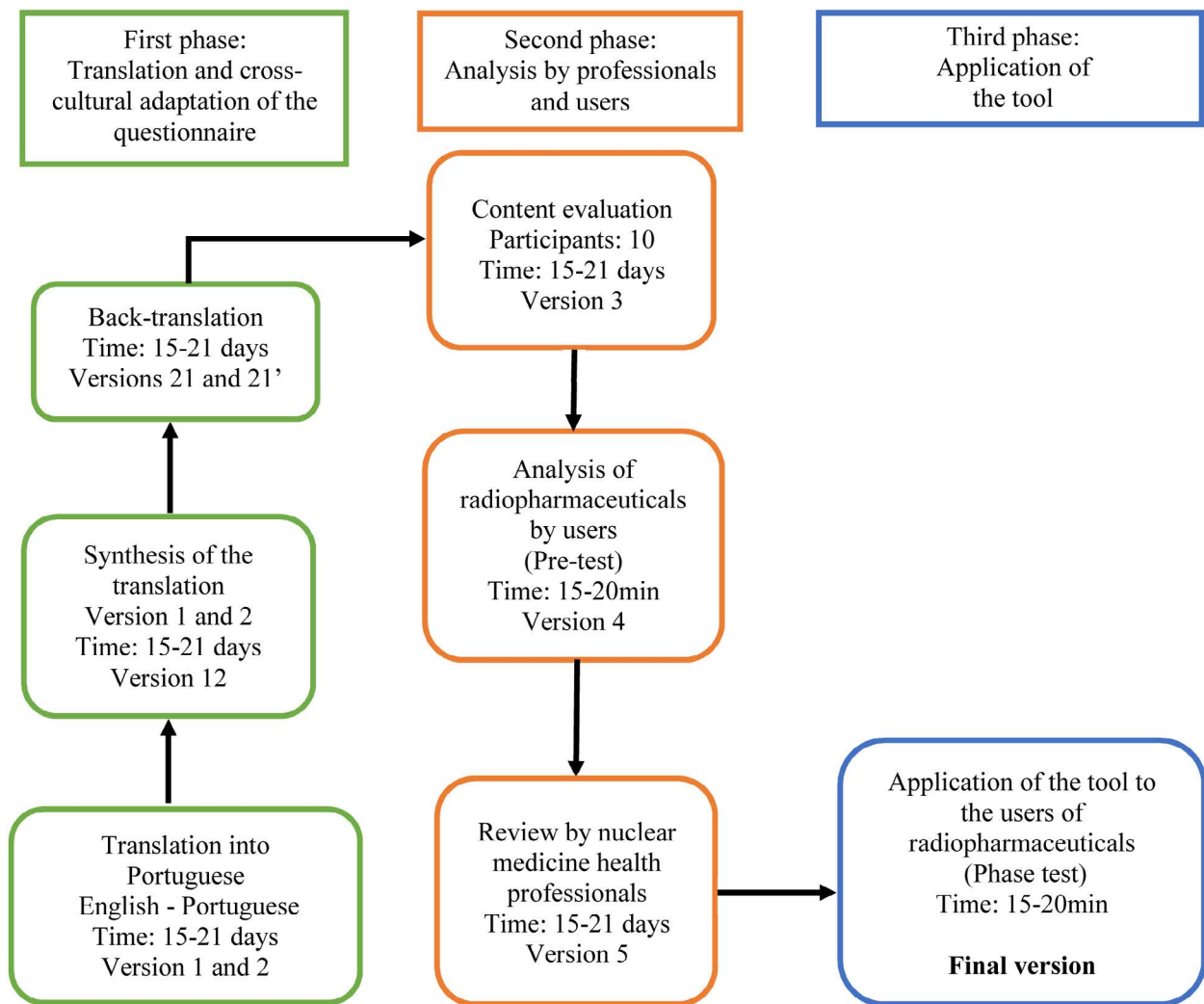


Figure 1. Cross-cultural translation, adequacy through the final version of the self-reported questionnaire of radiopharmaceuticals-related adverse events within the timeframe of each step

Upon the conclusion of the translation and cross-cultural adaptation, the questionnaire was applied to users of nuclear medicine. Enrollment was conducted at the waiting room of the exam, when the questionnaire was delivered to the participant and returned upon completion without intervention of the investigator.

The data were organized and analyzed through Microsoft Office Excel[®] expressed in descriptive statistics across every analysis of the tool¹⁴. Based on Delphi technique, simple statistics was applied to calculate the mean and percentage of each question for clarity and pertinence to reach the experts' consensus.

The algorithm Silberstein¹⁵ consisting in four categories of causality – not related, conditional, possible and probable – was utilized to categorize probabilities of causation. For that matter, data on the beginning of the adverse event and its occurrence in previous exams, status of the patient recovery and other possible causes of adverse events as the administration of interventionist agents or

patient-reported have been utilized. Current literature was utilized to determine whether conclusive previous reports about the adverse event existed or if it was the known response pattern¹.

The Ethics Committee of “*Universidade Federal Fluminense*” and of the National Cancer Institute (INCA) approved the study, reports number 5.230.506 and 5.336.064 (CAAE (submission for ethical review): 52192921.6.0000.5243 and 52192921.6.3001.5274), respectively, in compliance with Directives 466/2012¹⁶ and 510/2016¹⁷ of the National Health Council.

RESULTS

The evaluation of the first translation into Portuguese produced 34 comments about the choice and adjustment of the questions. Eight nuclear medicine expert health professionals participated of the second phase to evaluate the content. Two professionals, one male, mean age of 44

years old, were excluded for not delivering the evaluation in time. All of them had more than five years of experience in oncology and nuclear medicine and most of them (7) had intermediate or advanced experience in English language (Table 1).

Five judges suggested 85 changes in 35 questions of the version T1. Only two judges indicated 24 changes in version T2. Five judges suggested 60 changes in the English back-translation of versions T21 and T21' (Table 2).

The majority of the changes were suggested for version T12. Eight judges recommended 189 changes in 67 questions: typo errors (2), subject-verb agreement (7), change of word "adverse event" to "adverse effect" (14), delete words (15), change the words "physical changes" to "physical alterations" (28), include words (41) and change other words for better understanding (82). Of the 189 changes suggested, 68 were made in the tool (Table 2). In addition to the textual changes, structural changes in the body of the questionnaire were made to optimize the reading since the instrument was applied manually. Eventually, a version 3 was produced containing 63 questions for analysis by nuclear medicine users.

Continuing the second phase of the study, ten users of radiopharmaceuticals pre-tested version 3 of the questionnaire. Of these, eight were women, mean age of 58 years, three did not complete elementary school, two completed high school, three completed university and one, post-graduation. Only two questions successfully achieved the 3.9 score of clarity: "Have you ever submitted to a nuclear medicine test before?" and "Have any radioactive substance been administered to you during the exam?". One patient scored 2 in the last question, he reported he did not know what radioactive substance is. Although the other participants have scored 4 (fully understood) or 5 (fully understood and I have no doubts) for the same question, their response when answering the questionnaire was that they have not received any radiopharmaceuticals. Eventually, the final mean of clarity was 4.34 ± 0.34 .

Another issue brought up by the users was the necessity to add guidelines to the questions that should be skipped and not responded. For instance: if the user checks NO in question 13: "Have you ever submitted to any nuclear medicine test (scintigraphy and/or PET-Scan) before?", the user can skip the following questions because they were addressed to those who have at least used radiopharmaceuticals once. After this stage, the questionnaire reached version 4.

Later, ten nuclear medicine health professionals revised version 4, concluding the second phase of the study. Consensus was reached after the first round of evaluation.

The only recommendation made by seven judges was to add examples of exams close to the world "nuclear medicine" to facilitate the patient's understanding, which was accepted. Thus, version 5, the final version of the questionnaire to be applied to radiopharmaceuticals users, was produced.

221 users of radiopharmaceuticals were invited for the third phase, however, nine were minors and one did not accept to join, remaining 211 participants. The median of age was 58 (48 - 67) years and 136 (65%) were women. 157 participants (74%) claimed they completed high school, 11 (5%) did not respond. 159 (75%) reported they used at least one drug for continuous treatment (Table 3).

It has been observed that 129 (61%) participants reported pain/discomfort and 105 (49%) had anxiety and/or depression when they responded to questions about quality of life. The most utilized radiopharmaceuticals were [^{99m}Tc]Tc-MDP (technetium-99m methylene diphosphonate) (46%) and [¹⁸F]F-FDG (Fluorine-18 fluorodeoxyglucose) (42.2%) (Table 3).

Table 1. Characterization of the judges of the first version of the questionnaire of self-reported radiopharmaceuticals adverse events translated into Portuguese, Brazil, 2022

Characterization	N
Number of judges	8
Sex	
Male	1
Female	7
Age (Mean - SD)	44 (34 - 51)
Formation	
Physician	1
Nurse	2
Pharmacist	2
Biologist	2
Biomedical	1
Title	
Post-graduation	1
MSc	4
PhD	3
Time of experience in oncology (years), mean (SD)	9 (5 - 28)
Time of experience in NM (years), mean (SD)	6.5 (5 - 16)
Knowledge of english language	
Basic	1
Intermediate	3
Advanced	4

Captions: SD: standard deviation; NM: nuclear medicine.

Note: The results are referenced to the second phase of the study: Evaluation of the content by expert nuclear medicine health professionals.

Table 2. Evaluation of the questionnaire 'Experiences with Nuclear Medicine Examination' for self-reported radiopharmaceuticals adverse events, 2022

Versions	Number of questions evaluated	Number of suggestions	Number of judges
T1 ^a	35	85	5
T2 ^b	13	24	3
T12 ^c	63	203	8
T21 ^d	24	33	4
T21 ^e	36	45	5
Total	79	390	8
Changes of version T12	Number of questions evaluated	Number of suggestions	Number of judges
Typo	2	3	2
Subject-verb agreement	6	7	3
Change "adverse event" to "adverse effect"	11	14	4
Delete words	14	15	4
Change "physical changes" to "physical alterations"	29	28	2
Add words	37	42	4
Change word for better understanding	28	94	8
Total	NA	203	8

Captions: (a) T1: translation into Portuguese of the original instrument by the translator 1; (b) T2: translation into Portuguese of the original instrument by the translator 2; (c) T12: synthesis of the translations (T1+T2) by translator 3; (d) T21: translation of the synthesis (Portuguese) into English by the translator 4; (e) T21': translation of the synthesis (Portuguese) into English by the translator 5. NA: Not applicable.

Note: The results are referenced to the second phase of the study: Content evaluation by expert nuclear medicine health professionals.

Of the 211 participants, 18 (8.5%) reported at least one adverse event. Four (22.2%) were males, 13 (72.2%) reported anxiety or depression and 13 (72.2%) reported pain. Eight (44.4%) submitted to the exam for the first time and 12 (66.6%) used one or more drugs. Five (27.7%) reported adverse events that occurred in early exams but did not repeat in the exam when they were answering the questionnaire. Seven (38.9%) of these events were deemed as not-related, four (22.2%) as conditional, two (11.1%) as possible and five (27.8%) as probable according to Silberstein¹⁵. Radiopharmaceuticals involved in these events were [¹⁸F]F-FDG, technetium-99m labeled sodium phytate ([^{99m}Tc]Tc-PHYTATE), technetium 99mTC sestamibi ([^{99m}Tc]Tc-MIBI), I-131 Sodium iodide ([¹³¹I]I-Na) and [^{99m}Tc] Tc-MDP (Table 4).

DISCUSSION

The translation and cross-cultural adaptation of the tool are important processes to utilize questionnaires earlier validated in different sociocultural realities, not only idiomatic differences¹⁸. The critical evaluation of health professionals was essential to improve the questionnaire translated. Some items were altered and questions were

excluded or merged to improve the understanding and adequacy to the target-public. Because it was a printed material, it was necessary to restructure it physically and modify the initial explanatory text because the original was developed to be used electronically, which is unfeasible for the local reality where it was tested.

All the phases of the translation and cross-cultural adaptation were evaluated to produce a tool able to detect adverse events of users of a nuclear medicine service and later utilized by different persons and diverse education level. For that matter, ten expert of different ages and education levels analyzed the material to evaluate the understanding and guide the authors in relation to the structure of the questionnaire, when guidance to skip questions were added. As in other studies, this phase highlighted the participation of the target-public^{19,20}.

Some users did not know what radioactive substances were or whether they have been exposed to them while reading the question "Have any radioactive substance been administered to you during the exam?". Later, it was noticed that the majority responded that they received the contrast when answering the question "Did you receive X-rays during the study?", exposing the confusion between contrast and radiopharmaceuticals. These findings were



Table 3. Characteristics of the participants of the test phase of the questionnaire 'Experiences with Nuclear Medicine Examination' translated, 2022

Characteristics	Patients (n= 211)
Sex	
Male, n (%)	74 (35)
Female, n (%)	137 (65)
Age (years), median (25-75 percentile)	58 (48 - 67)
Weight (kg), median (25-75 percentile)	75 (63 - 85)
Height (cm), median (25-75 percentile)	163 (158 - 170)
Education	
No education, n (%)	12 (6)
Incomplete elementary school, n (%)	33 (16)
Complete elementary school, n (%)	28 (13)
High school, n (%)	82 (39)
Associate degree, n (%)	13 (6)
Complete college, n (%)	28 (13)
Post-graduation or equivalent, n (%)	4 (2)
Did not respond, n (%)	11 (5)
Patients who reported the use of at least one medication	159 (75)
EQ-5D^a (% of participants who reported problems)	
Mobility, n (%)	43 (20)
Self-care, n (%)	17 (8)
Regular activities, n (%)	64 (30)
Pain/discomfort, n (%)	129 (61)
Anxiety/depression, n (%)	105 (49)
EQ-health scale, median (25-75 percentile)	70 (60 - 90)*
First administration of radiopharmaceuticals	
Yes, n (%)	101 (48)
No, n (%)	72 (34)
Don't know or did not respond, n (%)	38 (18)
Radiopharmaceuticals administered	
[^{99m} Tc]Tc-MDP ^b , n (%)	97 (46)
[¹⁸ F]F-FDG ^c , n (%)	89 (42.2)
[^{99m} Tc]Tc-PHYTATE ^d , n (%)	13 (6.2)
[¹¹¹ In]In-DTPA-OCT ^e , n (%)	3 (1.4)
[¹²³ I]NaI ^f , n (%)	2 (0.9)
[^{99m} Tc]Tc-DMSA ^g , n (%)	2 (0.9)
[^{99m} Tc]Tc-MIBI ^h , n (%)	2 (0.9)
[¹³¹ I]NaI ⁱ , n (%)	1 (0.5)
[^{99m} Tc]Tc-DTPA ⁱ , n (%) (RENAL)	1 (0.5)
[^{99m} Tc]Tc-DTPA, n (%) (MUGA ^k)	1 (0.5)
Patients reporting at least one adverse event	18 (8.5)

Captions: (a) EQ-5D: EuroQol questionnaire; (b) [^{99m}Tc]Tc-MDP: technetium-99m methylene diphosphonate; (c) [¹⁸F]F-FDG: Fluorine-18 fluorodeoxyglucose; (d) [^{99m}Tc]Tc-PHYTATE: technetium-99m labeled sodium phytate; (e) [¹¹¹In]In-DTPA-OCT: 111In DTPA-octreotide; (f) [¹²³I]NaI: Sodium iodide I-123; (g) [^{99m}Tc]Tc-DMSA: technetium-99m dimercaptosuccinic acid; (h) [^{99m}Tc]Tc-MIBI: technetium 99mTC sestamibi; (i) [¹³¹I]NaI: Sodium iodide I-123; (j) [^{99m}Tc]Tc-DTPA: technetium-99m diethylenetriaminepentaacetic acid; (k) MUGA: synchronized scintigraphy of cardiac chambers.

Note: *Two participants reported health status=10; 20 did not fill the field. The results are referenced to the third stage of the study: Application of the tool.

noticed in the original article of the questionnaire, indicating that health literacy should be encouraged not only in Brazil⁷.

After the users of radiopharmaceuticals analyzed the tool, a new version was prepared by nuclear medicine experts when a consensus was reached in the first round of evaluation. The original study of Schreuder et al.⁷ analyzed otherwise, reason for which the results of the original tool were not compared with the Portuguese translated

version. However, the technique Delphi is applied in different studies of cross-cultural translation and was effective to reach an experts' consensus. This technique is economically feasible and, in the present study, was able to contribute to improve the clarity and pertinence of the questions in the conclusion of the questionnaire. Its application allowed to improve the questionnaire, clarify the questions, add examples of exams of nuclear medicine as bone scintigraphy, myocardial scintigraphy,

Table 4. Characteristics of patient-reported adverse events related to radiopharmaceuticals, 2022

Radiopharmaceuticals	Activity administered (Mbq)	Number of patients who reported AE ^a	Description of the AE by the patient	AE occurred in the current exam (the day the questionnaire was completed)	Causality	Frequency %
[^{99m}Tc]Tc-PHYTATE^b	74	6				
			1	Pain when administered	Yes	Not-related
			1	Sensation of swollen throat	No	Conditional
			2	Itching	No/Yes*	Not-related
			2	Burning	Yes	Not-related
[^{99m}Tc]Tc-MIBI^c	740	1				50.0
			1	Sleepiness	Yes	Conditional
[¹⁸F]F-FDG^d		6				6.7
			1	Dizziness	Yes	Possible
			1	Itching	Yes	Not-related
			1	Sensation of liquid in the right hand	No	Not-related
			1	Numb hand when administered	Yes	Not-related
			1	Nausea	No	Probable
			1	Vomit		Probable
			1	General malaise		Probable
			1	Cold	Yes	Not-related
			[^{99m}Tc]Tc-MDP^e		4	
3	Nausea	No/Yes*				Probable
1	Metallic taste in mouth	Yes				Possible
1	Fatigue	No				Conditional
[¹³¹I]NaI^f		1				100.0
			1	Nausea	Yes	Probable
			1	Loose skins in the mouth		Conditional

Captions: (a) AE: adverse event; (b) [^{99m}Tc]Tc-PHYTATE: technetium-99m phytate; (c) [^{99m}Tc]Tc-MIBI: technetium-99m sestamibi; (d) [¹⁸F]F-FDG: Fluorine-18 fluorodeoxyglucose; (e) [^{99m}Tc]Tc-MDP: technetium-99m methylene diphosphonate; (f) [¹³¹I]NaI: Sodium iodide I-131. Mbq: megabecquerel. **Note:** *One patient reported the occurrence of AE in the previous exam. The results are referenced to the third stage of the study: Application of the tool.



lymphoscintigraphy and PET-CT. There was no further questioning by the participants while they completed the phase test¹⁴⁻²³.

The phase test was important to evaluate whether the questionnaire would be able to collect not only possible adverse events but also the profile of the patients who attend the nuclear medicine service. While comparing the educational level of the participants with the level of the original questionnaire, the result was the opposite. The patients who completed high school, graduation or post-graduation account for 66%^{7,24}, a result expected because the original article was elaborated in a developed country with high educational level (81% of the adults between 25 and 64 years of age completed high school, above the mean of the OECD of 79%), unlike Brazil, a developing country where only 57% of the 25-64 years adults have completed high school. Therefore, adapt the tool for a specific population considering social, cultural and idiomatic questions is important.

Few participants reported adverse events at the test and only one adverse event was possibly related. The reference article presented the double of adverse events, however, methodological differences between the present study and the original did not allow the comparison of the results obtained during the application of the questionnaire. The study sample was smaller than the original and data were collected at the exam and were not reproduced seven days later. In addition, the original study evaluated adverse events of a larger number of radiopharmaceuticals⁷.

In addition, the frequency of adverse events found in the present study is higher than former studies with radiopharmaceuticals^{1,25,26}. The Brazilian study by Almeida et al.⁶ interviewed users of radiopharmaceuticals and was able to identify three adverse events in total in only 1.8% of the patients, showing that the tool applied in the present study met the objectives of identifying adverse events of radiopharmaceuticals.

Silberstein algorithm was the only one utilized to evaluate causality in the present study, however, more studies are necessary to evaluate the concordance and correlation of this algorithm compared with Naranjo's in relation to identification of causality of radiopharmaceuticals-related adverse events. It is difficult to determine a causal relation between the suspicious medication and the adverse event and despite some algorithms are frequently utilized in pharmacovigilance, they should not replace a full examination to evaluate an individual in face of an unexpected event⁸. Patient-reported adverse events with possible and probable causality are found in the literature. The majority of studies with radiopharmaceuticals adverse events is related to case studies with highly severe events as

anaphylactic shock that lead to admission or longer length of hospital stay^{3,27}.

The evaluation and validation of the instrument are continuous processes with possibilities of changes of interpretation over time²⁸. But it was possible to verify through the questionnaire that the users were able to identify the symptoms presented after the administration of the radiopharmaceutical and manage them early and accordingly, showing that the questionnaire was effective.

The reduced number of the patients during pre-test is one of the study limitations. Although a small sample can reveal critical problems, education in Brazil is heterogeneous. According to "*Instituto Brasileiro de Geografia e Estatística (IBGE)*" 35.2% of the 25-year old population or older was concentrated in the levels without education or incomplete elementary school in 2022. This reality hinders the understanding of health recommendations, including adverse events, in addition to difficult of access to preventive programs, early diagnosis and immediate proper treatment^{23,29,30}. Additionally, potential biases of the phase test could have happened since it was not possible to observe whether there was erroneous completion of the questionnaire or partially unanswered questions.

CONCLUSION

The cross-cultural adaptation of the questionnaire into Portuguese identified self-reported radiopharmaceuticals-related adverse events and was effective in view of the cultural adaptations. Further studies to evaluate acute or late adverse events related to radiopharmaceuticals utilizing representative samples of other nuclear medicine services across different regions and populations of the country are necessary to disseminate the knowledge related to this practice.

CONTRIBUTIONS

Maria Carolina Peçanha Fernandes, Priscilla Brunelli Pujatti and Sabrina Calil-Elias contributed substantially to the concept and design of the study, acquisition, analysis and interpretation of the data, writing and critical review. Mahanna Vanzeler Vaz contributed to the conception and design of the study, acquisition, analysis and interpretation of the data. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

All the content underlying the text is contained in the manuscript.

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